IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Jacob Bar-Tana and Ihor Bersky

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For: METHODS OF ADMINISTERING 3,3,14,14 TETRAMETHYL HEXADECANE 1,16 DIOIC ACID

Declaration of Jacob Bar-Tana, M.D, Ph.D
Under 37 C.F.R. § 1.132

I, Jacob Bar-Tana, hereby declare and state as follows:

I am a doctor of medicine and a doctor of philosophy and currently serve as Professor of Biochemistry in the Department of Human Nutrition and Metabolism, Hebrew University Medical school, Jerusalem, Israel. I also am the managing director of Syndrome X Ltd., the assignee of record of the above-identified patent application. My Curriculum Vitae is attached hereto (**Annex A**).

I am a co-inventor of the invention which is the subject of the above-identified application.

The invention recited in the claims being amended concurrently with the filing of this Declaration relates to a method for the treatment of dyslipoproteinemia in a human subject in need thereof comprising periodically orally administering to the

human subject 3,3,14,14-tetramethylhexadecane-1,16-dioic acid (also known as Medica 16 or M16) in a dose range of from about 30 mg per day to about 400 mg per day.

The following is a description of the study conducted and the results obtained in a pilot Phase IIa human clinical study aimed at verifying the safety and efficacy of Medica 16 administered for up to 38 weeks for treating dyslipoproteinemia and insulin resistance in obese, dyslipoproteinemic, insulin resistant, non-diabetic male subjects.

Study Design: patients were selected from a pool of patients who were in a follow-up program after the completion of treatment for dyslipoproteinemia, obesity, and diabetes. Subjects who ultimately entered the study were selected as based on three screening stages.
In the first stage the following subjects were selected based on the following criteria: (1) males, aged 45-60 years old; (2) not currently on medication for diabetes, hypertension, or dyslipidemia; (3) family history of hyperlipidemia, and/or diabetes, and/or ischemic heart disease; and (4) at least three of the following criteria: BMI > 28kg/m^2; HDL-C <35mg%; plasma cholesterol >200 mg%; plasma triglycerides >240mg%. Exclusion criteria were hepatic, renal, digestive tract, or endocrine dysfunction, coagulative disorders, or a malignancy.

Qualified subjects then underwent an oral glucose tolerance test (OGTT - measurements of glucose and insulin levels at 0, 60 and 120 minutes after the administration of 75g of glucose). Fifty two subjects classified with Impaired Glucose Tolerance (IGT) underwent the OGTT. Of these subjects, twelve who were classified were considered as possible study subjects. Of these twelve possible subjects, 5 met all inclusion criteria and were entered into the study. A sixth subject

was entered into the study after completing one cycle of treatment. Thus there were 6 evaluable subjects at study's end.

Treatment with M16 was in an escalation dose fashion, with at least 3 dose levels per subject, and treatment for at least 4 weeks at each dose. The dose range was 30 to 600 mg once daily. Placebo tablets contained 200 mg lactose powder monohydrate; the strength of the M16 tablets was 30, 100 or 200 mg (net drug); the targeted doses were 30, 100, 200, 400 or 600 mg/day.

Table 1 presents the efficacy of M16 in lowering the plasma triglycerides and cholesterol levels of the M16-treated subjects. The data in Table 1, summarized in the right column for all patients and the respective doses, indicate that M16 at doses of 30-200 mg/day decreased triglycerides by 42-53% from base line. Dose escalation to 400 mg/day provided essentially the same decrease and did not produce any further significant decrease in TG, implying that maximal efficacy for the TG lowering effect of M16 was reached using the 200 mg/day dose.

Table 1: Efficacy Summary – Effects of M16 on Serum Lipids

Dose (mg/day)	Parameter	Mean Percent Decline from Mean Base line Values						Mean ± SD
		Subject						
		101	102	103	104	105	106	
30	TG					41.3 (8)	55.7 (7)	48.5
	Ch					13.1	6.4	9.7
100	TG					47.5 (5)	59.0 (6)	53.2
	Ch					7.3	9.1	8.2
200	TG	43.6 (5)	6.4 (5)	54.4 (4)	25.1 (5)	53.6 (6)	71.4 (7)	42.4±23.3
	Ch	11.0	0.4	21.5	22.4	13.4	7.4	12.7±8.4
400	TG	36.0 (8)	6.9 (4)	57.6 (4)	37.7 (8)			34.5±20.9
	Ch	11.0*	7.6*		22.9			4.3
500	TG		1.8* (5)					1.8*
	Ch		6.8*					6.8*
600	TG		8.1 (7)	59.1 (9)				33.6
	Ch		1.8	18.3				10

TG – triglycerides; Ch – cholesterol; ( ) = number of treatment weeks at given dose;

* = parameter values increased from base line at given dose

The effect of M16 on sensitization to insulin was studied by intravenous bolus injection of a glucose load followed by measuring plasma glucose and plasma insulin over time during the next 20 min. Sensitization to insulin was evaluated by calculating the S_R ratio [defined as K_{Glu} / $AUC_{ins(0-20)}$ where K_{Glu} (in min^{-1}) is the elimination constant of plasma glucose and $AUC_{ins(0-20)}$ is the integrated plasma insulin levels during the measurement period]. The S_R value was determined for all 6 subjects treated with the 200 mg/day dose, 4 subjects treated with the 400 mg/day dose, and for 2 subjects treated with the 600 mg/day dose. Table 2 presents the results of the effect of the M16 treatment on the S_R parameter for each subject and respective M16 dose.

The data in Table 2 indicate that the 200mg/day dose of M16, which was the optimal dose of M16 for the TG-lowering effect in these patients, resulted in a non-**significant** 1.6-1.7-fold increase in sensitization to insulin (Index 2) as defined by the S_R value, when compared to placebo. Moreover, in contrast to the hypolipidemic efficacy of M16, significant sensitization to insulin by M16, amounting to a 2.5-2.8-fold increase in S_R when compared to placebo, required using M16 doses of 400-600 mg/day (Index 1). Thus, sensitization to insulin by M16 at physiological insulin levels required higher doses of M16 than were required for reduction of plasma triglycerides levels.

Table 2: Effect of M16 on S_R in response to IV-glucose loading

Subject	Placebo	S_R in response to M16 dose (mg/day)					Index 1 (%)	Index 2 (%)
		30	100	200	400	600		
101	-0.025	-	-	-0.029	-0.023	-	92	116
102	-0.031	-	-	-0.038	-0.037	-0.076	245	126
103	-0.009	-	-	-0.014	-0.009	-0.038	422	156
104	-0.019	-	-	-0.016	-0.048	-	253	84
105	-0.014	-0.02	-0.024	-0.028	-	-	200	200
106	-0.011	-0.031	-0.031	-0.03	-	-	273	273
Mean ± SD, all participants							248 ± 44*	159 ± 28
Mean ± SD, IGT subjects (101 excluded)							279 ± 17*	168 ± 32

S_R expressed as x 10^3; * significance ($p<0.05$) relative to placebo; S_R units=ml μU^{-1} min^{-2}; Index 1 represents the effect of the highest M16 dose administered to each subject; Index 2 represents the effect of the 200 mg/day dose of M16

Both (A) the specific dose range of M16 that was effective in reducing lipids and (B) the fact that this dose range was different from the dose range of M16 that was effective in providing sensitization to insulin could not have been predicted prior to the Phase IIa Study.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issuing from the application referenced herein.

Date: January 6th 2011 By: J. Bar-Tana

Jacob Bar-Tana

CURRICULUM VITAE

Jacob Bar-Tana

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Israel 91120. Tel-

Major Research Interests:

Metabolic Syndrome; Nuclear receptors; Colon and Breast cancer; Drugs for the Metabolic Syndrome and its diseases

Educational Background:

Academic Background:

1966 : Hebrew University Medical School.
M.D.

1972 : Hebrew University Medical School.
Ph.D. (*Summa cum Laude*).

Post-graduate Studies:

1972–1975: Department of Biochemistry, University of Wisconsin;
Fox Chase Institute of Cancer Research, Philadelphia;
Department of Biochemistry, UC Berkeley.

Professional Appointments:

1976–1988: Department of Biochemistry,
Hebrew University Medical School

1988 : Professor of Biochemistry, Hebrew University

1988–1991: Head, Department of Physiological Biochemistry,
Hebrew University Medical School

1989–1994: Head, Life Sciences and Medicine Section of the Israel Science Foundation (*administered by the Israel Academy of Sciences and Humanities*)

1992–2002: Head, Department of Human Nutrition and Metabolism,
Hebrew University Medical School

1992–2009: Chairman, Human Nutrition and Metabolism Curriculum,
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